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# Total Synthesis of the Salicylate Enamide Macrolide Oximidine II[1]

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Oximidines I (**1**)[1] and II (**2**) (Figure 1) are closely related metabolites isolated from *Pseudomonas sp.* Q52002 which display potent antitumor activity. Relative and absolute stereochemistry assignments were based on extensive NMR studies, including modified Mosher ester analysis.[2] Recently, **1**, **2**, and other salicylate enamide macrolides such as the lobatamides[3] and salicylihalamides[4] have been shown to selectively inhibit mammalian vacuolar-type proton ATPase.[5] Both **1** and **2** contain a highly unsaturated 12-membered macrolactone and (*Z*)-enamide side chain, differing only in epoxidation at C12−C13. Oximidine II possesses an (*E*,*Z*,*Z*)-conjugated triene within the macrolactone, which is very uncommon in natural products.[6] Recent reports have documented approaches to the enamide side chain[7] and core structures[8] of the oximidines. Herein, we report the first total synthesis of (-)-oximidine II (**2**), employing an uncommon ring-closing metathesis of a bis-diene to construct the macrocyclic triene core.[9]

Our retrosynthetic analysis of oximidine II is shown in Figure 2. We planned to utilize copper-mediated amidation[10] of (*Z*)-vinyl iodide **3** and amide **4**[10a] for the late-stage introduction of the (*Z*)-enamide side chain. To construct the macrocyclic triene core, we first considered ring-closing metathesis (RCM)[11] of bis-diene substrate **5**. We anticipated that the strained, macrocyclic triene would be prone to ring-opening metathesis and therefore hoped to form the ring using kinetic control[12] by alteration of the protective groups ($P_1$−$P_3$) and diene substitution pattern of **5**.

We initiated our studies to prepare terminal diene fragments **6** and **7**.[13] The synthesis commenced with asymmetric allylboration[14] of aldehyde **8**[15] to afford **9** as a single diastereomer in 80% yield (90% ee) (Scheme 1). The secondary alcohol was silylated, and the terminal olefin was oxidized to aldehyde **10** by a two-step procedure. Using Yamamoto's protocol,[16] we converted aldehyde **10** to the desired *cis*-diene **6** after desilylation. Treatment of **6** with NaHMDS, followed by addition of acetonide **7** (prepared by Stille coupling[17] of triflate **11**[10b] and dienyl stannane **12**[18]), afforded bis-diene **13**, which was silylated to provide compound **14**. Attempted MOM deprotection of **14** with $BBr_3$ unexpectedly afforded the 1,3-dioxepan **15**, which was desilylated to phenol **16**.

With substrates **13**−**16** in hand, we examined their reactivity in RCM reactions.[19] Treatment of all substrates with Ru catalyst **17** afforded products resulting from reaction of the *trans*-diene and gave no observable further conversion.[20] When treated with catalyst **18**, substrates **13** and **14** reacted with the *trans*-diene and gave no further conversion ($CH_2Cl_2$, reflux, 3 h). These results suggested that the *trans*-diene of substrates **13** and **14** was the initiation site for RCM, but that macrocyclization was nonproductive. Constrained substrates **15** and **16** afforded oligomeric products (20 min). In addition, HPLC-MS analysis indicated trace formation of 10-membered ring product(s) for substrate **16**, but no desired macrocyclic triene.

On the basis of these results, we next incorporated a *trans*-methyl group on the more reactive *trans*-diene in an effort to initiate the RCM at the terminus of the *cis*-diene. Synthesis of second

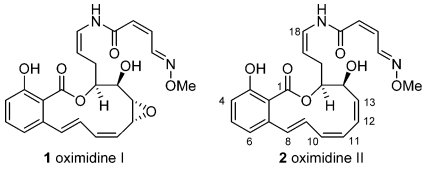



***Figure 1.*** Structures of oximidines I (**1**) and II (**2**).

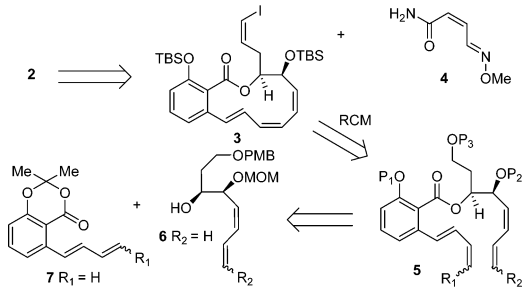
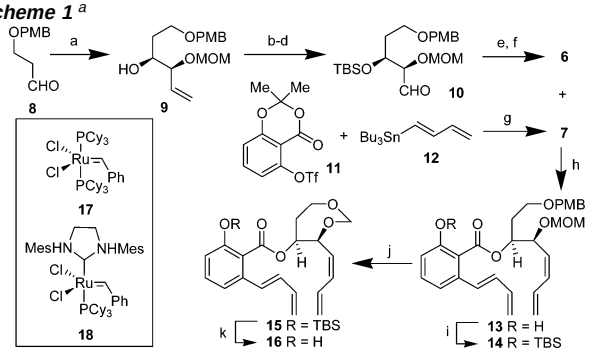



***Figure 2.*** Retrosynthetic analysis of oximidine II.

***Scheme 1*** [a]



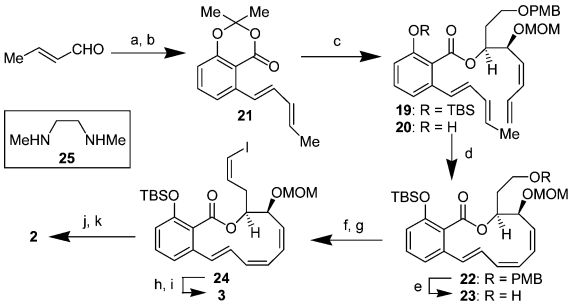
[a] Conditions: (a) allyl methoxymethyl ether, $^s$BuLi, (+)-$Ipc_2BOMe$, $BF_3{\cdot}OEt_2$, −78 to 0 °C, 80%; (b) TBSCl, imidazole, DMF, 94%; (c) cat. $OsO_4$, NMO, THF/$H_2O$; (d) $K_2CO_3$, $Pb(OAc)_4$, MeOH, 0 °C; (e) $^t$BuLi, allyldiphenylphosphine, $Ti(O^iPr)_4$, THF, −78 to 0 °C; then MeI; (f) TBAF, THF, 71% (four steps); (g) $Pd_2dba_3$, $P(2\text{-furyl})_3$, LiCl, DMF, 60 °C, 89%; (h) **6**, NaHMDS, then **7**, THF, 0−25 °C, 95%; (i) TBSCl, imidazole, $CH_2Cl_2$, 95%; (j) $BBr_3$, $CH_2Cl_2$, −78°C, 35%; (k) TBAF, THF, 0 °C, 60%.

generation substrate **19** (Scheme 2) was initiated by homologation[21] of (*E*)-crotonaldehyde to afford a dienyl stannane which coupled with **11** to furnish the desired (*E*,*E*)-diene **21**. Treatment of **6** with NaHMDS, followed by addition of **21** and silylation, provided bis-diene **19** in a one-pot procedure. After considerable experimentation, we found that treatment of **19** with 5 mol % **18** in $CH_2Cl_2$ (2 mM, reflux, 70 min) afforded the oximidine II core **22** in 48% yield (one recycle) accompanied by oligomeric products. Extended reaction time resulted in decomposition of both starting material and product. It should be noted that under the same condition, phenol **20** did not undergo RCM but afforded only oligomeric products. Monte Carlo conformational searches on model compounds **A** and **B** (Figure 3) show a potential rationale for control of the C10−C11 olefin geometry by protection of the phenol.[10b,13]



10.1021/ja034030o CCC: $25.00 

***Scheme 2*** [a]




[a] Conditions: (a) $CrCl_2$, DMF, $Bu_3SnCHBr_2$, THF; (b) **11**, $Pd_2dba_3$, P(2-furyl)$_3$, LiCl, DMF, 80 °C, 61% (two steps); (c) **6**, NaHMDS, THF, 0−25 °C; then TBSCl, imidazole, 100%; (d) **18** (5 mol %), $CH_2Cl_2$, reflux, 48% (one recycle); (e) DDQ, $CH_2Cl_2/H_2O$ (10/1), 0−25 °C, 93%; (f) PDC, 4 Å mol. sieves, $CH_2Cl_2$; (g) $(Ph_3P^+CH_2I)I^-$, NaHMDS, THF, −78 to 25 °C, 60% (two steps); (h) $CBr_4$, $^i$PrOH, 75 °C, 83%; (i) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 to 0 °C, 93%; (j) **4**, CuTC, **25**, $K_2CO_3$, 50 °C; (k) HF−pyridine/pyridine, THF, 44% (two steps).

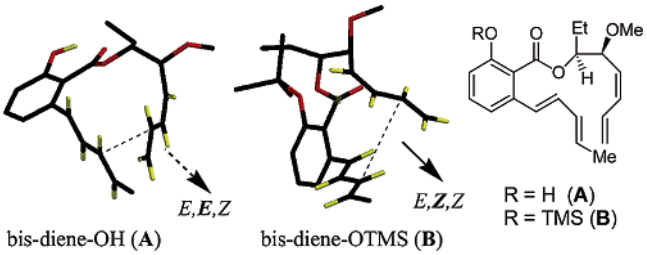



***Figure 3.*** Representative reactive conformers of ring-closing metathesis substrates **A** and **B** (dashed lines indicate newly formed C10−C11 bonds).

For phenol substrate (**A**), the salicylate carbonyl maintains near planarity with the aromatic ring, leading to the predicted formation of a high energy and potentially reactive (*E*,*E*,*Z*)-triene.[22] In contrast, silylation of the phenol forces the carbonyl out-of-plane from the benzene ring;[23] subsequent rotation of the C8−C9 bond affords the desired (*E*,*Z*,*Z*)-macrocyclic triene.

To advance **22** to a substrate for copper-mediated vinylic amidation, the PMB ether was removed (DDQ), and the resulting alcohol **23** was oxidized with PDC. Wittig olefination using the Stork/Zhao protocol[24] led to **24** as a single olefin isomer. The MOM protecting group was cleanly removed under mild, acidic conditions ($CBr_4$, $^i$PrOH),[25] and the resulting alcohol was reprotected to afford (*Z*)-vinyl iodide **3**.

Amidation of **3** with oxime amide **4** using conditions reported earlier for (*E*)-vinyl iodides[10a] led to low yield due to competitive elimination under basic conditions. After a model study involving evaluation of various ligands and bases,[22] we found that **3** coupled smoothly with **4**, employing stoichiometric amounts of CuTC[26]-*N*,*N*′-dimethyl-ethylenediamine (**25**)[27] and $K_2CO_3$ as base (50 °C). Oximidine II (**2**) was obtained after desilylation (HF−pyridine/pyridine) with retention of olefin geometry. Synthetic **2** was confirmed to be identical to natural oximidine II by the $^1$H and $^{13}$C NMR spectra, mass spectrum, $[\alpha]_D$, HPLC, and TLC $R_f$ values in three solvent systems.

In summary, the first enantioselective synthesis of the salicylate enamide macrolide oximidine II has been accomplished using the RCM of a well-defined bis-diene substrate to construct the unusual macrocyclic triene core, and stereoselective copper-mediated amidation of a (*Z*)-vinyl iodide to construct the enamide side chain. Further synthetic studies on the oximidines and their biological evaluation will be reported in due course.

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**Supporting Information Available:** Experimental procedures, theoretical calculation results, and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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